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NEW OBSERVATIONS IN THE HISTOPATHOLOGY OF ERYTHEMA NODOSUM

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Erythema nodosum presents variable clinical and histologic patterns of response in the vessels, septa, and fat lobules of the subcutaneous tissue. Acute or chronic phlebitis with hemorrhage may be commonly observed; acute panniculitis is observed in foci, but at times it may be the principal histologic feature; lymphocytic infiltration of fat lobules is often found, and lymphoid nodules are not infrequent; rarely, chronic granulomatous lesions involve septa or fat lobules; and proliferative lipocyte response may be observed. Because these variable histologic patterns may be coexistent, excision biopsy and multiple sections are necessary to recognize them. The variable histologic features correlate with the different clinical forms: acute nodular, chronic nodular, migrating plaque lesion, cellulitis, and the rare suppurative form. This variety of panniculus response in erythema nodosum can be explained on the basis of host-tissue response to a delayed hypersensitivity reaction to an antigenic stimulus.

Erythema nodosum may be defined clinically as an immunobiologically reactive inflammatory syndrome involving the small vessels of the subcutaneous tissue and dermis which produces crops of red nodules of short duration. Recent study has emphasized that, in addition to its classic relationship to tuberculosis and streptococcal disease, erythema nodosum is significantly related to sarcoidosis and Yersinia [1,2]. Many viral, bacterial, and fungal diseases are associated with this reaction, often under circumstances that have raised the question of whether the infectious agent or the drug therapy was responsible for the reaction [3,4]. The diagnosis of erythema nodosum is based mainly on the sudden appearance of the lesions, their clinical appearance as localized or diffuse areas of redness, and the rapid resolution of the inflammation with therapy of bed rest and wet dressings. The histopathologic features have been considered diagnostic but not specific [4–9].

In our recent studies of panniculitis, some problems in the diagnosis of erythema nodosum have become apparent—we found erythema nodosum associated with acute and chronic panniculitis. We wish to demonstrate the polymorphous and focal histologic nature of erythema nodosum, involving as it does vessels, septa, and panniculus and to indicate the many avoidable problems that arise.

The first problem is one of sampling the dermis and subcutaneous tissue. Excision biopsy must be the accepted standard for the histopathologic study of subcutaneous inflammation. In erythema nodosum, the punch biopsy technique has been used frequently because of its ease and general availability, in contrast to the time-consuming effort required to biopsy by the excision technique. However, in our experience, less than half of the punch biopsies in erythema nodosum show significant pathologic change and, of these, only 10 to 20% can be interpreted reliably. Such a significant failure rate should discourage clinicians from using the procedure and should explain why dermatopathologists have been so dissatisfied with small samples of a variegated pathologic picture. The clinical course of the patient has been a more reliable guide to diagnosis than have pathologic findings obtained under limiting circumstances.

An additional fundamental problem in using pathologic findings in defining the range of changes in the erythema nodosum reaction has been the choice of study material. Most studies have rejected cases in which the histology did not fit clearly defined limits accepted by the author. Since this is a natural desire—to have a "pure" case group for study—in studying a polymorphous pathologic process, cases at the edge of easy recognition are excluded. While studying 51 cases of acute panniculitis, we discovered that half were typical clinical examples of erythema nodosum (confirmed by follow-up; unpublished data). While reviewing granulomatous panniculitis, we also discovered 5 clear-cut cases of recurrent erythema nodosum [10]. Examination of fat necrosis and superficial thrombophlebitis also demonstrated a few cases in which the crops were of short duration—red nodules that could be described best in terms of erythema nodosum. Our purpose in this report is to show the broad range of changes in vessels, septa, and panniculus that may be observed in erythema nodosum.

The polymorphous nature of erythema nodosum pathology (Tab. I) indicates the variety of vessel disease and its consequences, the perivascular septal inflammation and reaction, and finally the

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panniculitis that can occur. The pathologic process must be considered primarily as vascular inflammation, and most changes are related to this. However, the coexistence of hemorrhage, acute panniculitis or fat necrosis (or both), and granulomas is (or should be) part of the expected microscopic findings of this reaction. Any individual feature may be predominant in a given area of a biopsy specimen, so that multiple sections are necessary to recognize the variations and localizations of the pathologic process. The acute reactions involve polymorphonuclear leukocytes, and the chronic reactions demonstrate lymphocytes and varied numbers of histiocytes. Such histopathologic changes represent the variable reactions by which the pattern of erythema nodosum is displayed at both clinical and microscopic levels.

VESSEL INFLAMMATION

The veins are the major vessels involved in erythema nodosum. Löfgren and Wahlgren [8] observed that 40% of patients with erythema nodosum had thrombophlebitis, and our experience agrees with this. If a large biopsy specimen is taken and enough sections are cut, a large vein with acute inflammation will be frequently observed. The reaction may be acute and may demonstrate acute thrombophlebitis with complete destruction of the vessel wall and a red blood cell–polymorphonuclear cell coagulum in the lumen (Fig. 1*A*). The vessel wall is permeated by polymorphonuclear leukocytes and red blood cells. However, the vascular inflammation usually is characterized by a lymphocytic cellular infiltration. All the veins in the dermis may be surrounded and permeated by lymphocytes. The larger subcutaneous veins may show a similar focal change. Frequently, the vein may demonstrate extensive endothelial proliferation and separation of the muscular laminae of the vein walls by a mixed inflammatory infiltrate composed of lymphocytes, histiocytes, and occasional polymorphonuclear leukocytes. The inflammation may progress to a granuloma, with luminal and mural histiofibroblastic response and often including giant cells (Fig. 1*B*). This is the natural evolution of thrombophlebitis, and it is repeated in erythema nodosum. Final fibrosis of the vessel wall and lumen may be observed. We emphasize that these histopathologic differences in vessels represent a range that may be found sequentially in one biopsy specimen or may be observed individually. It is this range of vascular reaction that must be considered in relation to other histopathologic observations.

TABLE I. *Histopathology of erythema nodosum*

Phlebitis
Lymphocytic
Polymorphonuclear leukocytic
Hemorrhagic
Septal inflammation
Acute
Chronic, granulomatous
Panniculitis
Acute
Chronic, granulomatous

The acute vascular lesion gives rise to septal hemorrhage and hemorrhage in the subcutaneous fat lobules. While such hemorrhage has long been recognized clinically as a major feature of erythema nodosum (that is, the synonym, erythema contusiformis), pathologic description has not emphasized this. It is not unusual to find a given histologic section of erythema nodosum demonstrating diffuse hemorrhage with mild, perivascular inflammation. We believe that, microscopically, hemorrhage may be a major feature of erythema nodosum and may be associated with

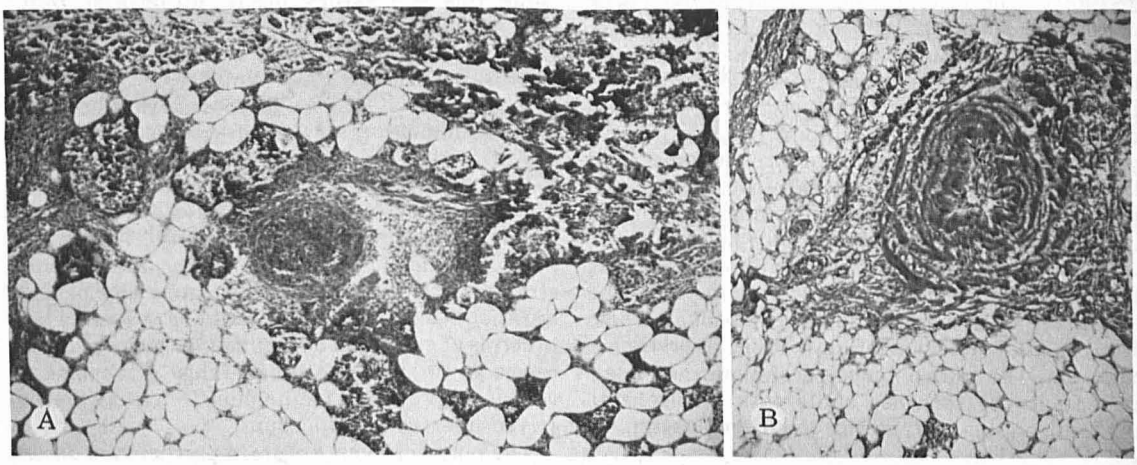

FIG. 1. Acute thrombophlebitis in erythema nodosum. *A:* Note peripheral inflammation of fat lobule related to vessels (H & E, ×12). *B:* Marked endothelial cell swelling and proliferation, with mild lymphocytic inflammatory infiltrate of vein wall muscle layers (H & E, ×12).

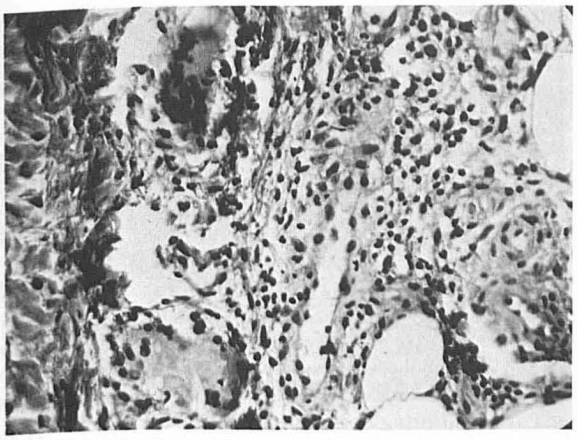

FIG. 2. Lymphohistiocytic infiltrate at edge of fat lobule, showing giant cells and mild lymphocytic vascular inflammation (H & E, ×140).

other pathologic findings or may be the unique, but nonspecific, observations of a given biopsy sample.

SEPTAL INFLAMMATION

The major blood vessels in the fat travel in the septa of the fat lobules, and because the inflammation is related to the vessels primarily, it is observed in the septal connective tissue around the vessels. Acute septal inflammation with necrosis may appear at first to be a primary focal infection (or similar to one), producing necrosis of connective tissue in a mass of polymorphonuclear leukocytes. In all instances, multiple sections reveal the primary vessel involvement. Only one septal area is usually involved, emphasizing the focal vascular change. Hemorrhage may occur after the development of the acute septal inflammation and may be seen adjacent to it. In many patients, the perivascular septal inflammation is lymphocytic and septal invasion by chronic, round cells is observed. The lymphohistiocytic reaction may be observed in an acute lesion when the lesion biopsied is only 24 hours old. As the lesions develop, histiocytic and giant cell changes occur (Fig. 2). The radially organized histiocytes may form a micronodule (the Miescher granuloma), which may be observed in the septa or in the periphery of a fat lobule. The connective tissue of the septa may demonstrate a fibrinoid change, and associated with this change is a septal, granulomatous inflammation composed of histiocytes, lymphocytes, and giant cell masses. Caseation is not observed, but the inflammatory changes produce necrobiosis of the adjacent connective tissue. As the inflammation encroaches on the fat lobules, the fat lobule vessels proliferate, forming granulation tissue with acute infiltration of polymorphonuclear leukocytes and perivascular fibrosis. This septal inflammation can heal, with only fibrosis and thickening of the septum or with massive scar formation and obliteration of fat lobules.

PANNICULITIS

The inflammation of the fat lobules in erythema nodosum is usually seen at the periphery. The central area is frequently spared the pathologic change, and this has been considered to be significant for the diagnosis of erythema nodosum. All of the changes of inflammation—acute polymorphonuclear leukocyte or lymphocyte inflammation (or both) and granulomatous, necrobiotic, degenerative, and vascular proliferative changes—are observed in the periphery of the fat lobule. Associated findings of hemorrhage and, more rarely, plasma cell infiltration and fat cell proliferation are also observed. Significant primary fat necrosis is not found.

ACUTE PANNICULITIS

The fat lobule may be replaced completely by acute panniculitis. This replacement may consist of masses of polymorphonuclear leukocytes and mononuclear cells (Fig. 3*A*). Associated with this acute cellular infiltration is necrosis of the cellular infiltrate itself and secondary necrosis of the fat lobule. The inflammatory cells may replace most of the fat lobule, and the remaining fat cells may enlarge, becoming microcystic (Fig. 3*B*). Fat cell proliferation may not be observed. Proliferative fat cell reaction does occur, however, in the panniculitis of erythema nodosum. The immature fat cells may proliferate in a sea of acute and chronic inflammation of the fat lobule (Fig. 3*C*).

A more typical form of panniculitis in erythema nodosum is the lymphocytic infiltration. This apparently represents an extension of the perivascular and septal lymphocytic vasculitis, principally involving veins. The lymphocytes may encircle each fat cell in a complete necklace, and polymorphonuclear leukocytes or nuclear dust may be associated with the infiltration. This form of inflammation is frequently less destructive and more focal, though most of a fat lobule may be involved. Secondary fat necrosis associated with the lymphocytic inflammation may occur, with giant cells and microcyst formation. The blood vessels of the fat lobule itself usually show minimal change until the entire lobule is replaced by inflammation.

CHRONIC GRANULOMATOUS PANNICULITIS

The lymphocytic inflammation usually blends into a patchy, lymphohistiocytic, granulomatous reaction. The macrophage–histiocyte reaction is no longer manifested as the occasional microscopic Miescher nodule but becomes large granulomatous masses and nodules (Fig. 4). These granulomatous or tuberculoid nodules of epithelioid cells are surrounded by lymphocytes, although occasionally the nodules are relatively free of lymphocytes, as in sarcoid tubercles. Caseation is not observed, and no bacilli are observed in special stains or cultures. Fluoroscopy and polarization do not reveal unusual substances. No asteroid or Schaumann's bodies are

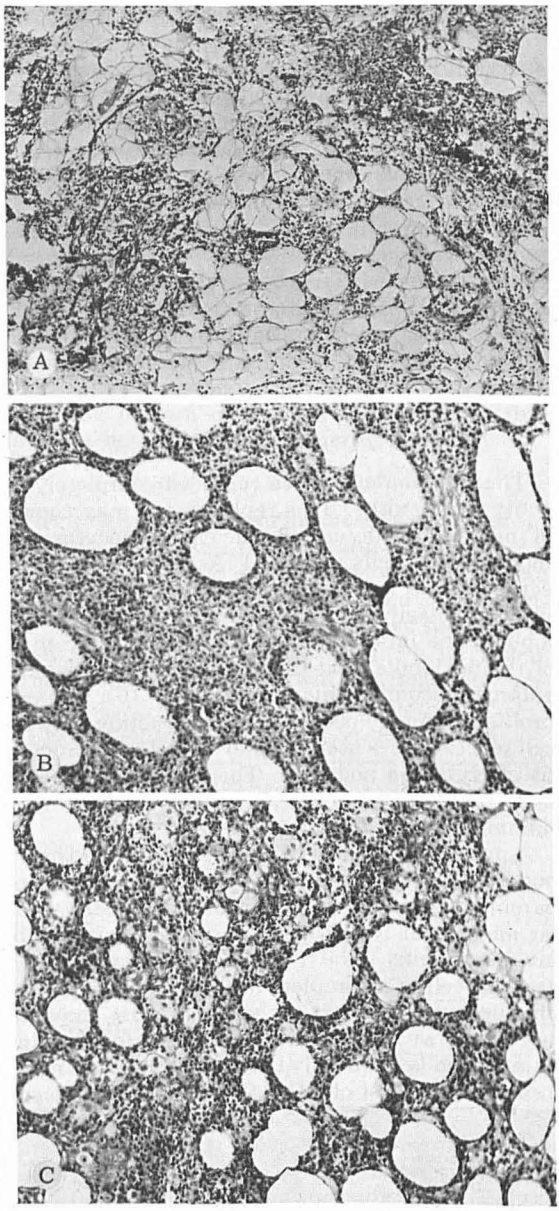

FIG. 3. *A:* Infiltration of fat lobule with acute inflammatory cells and mild secondary fat necrosis (H & E, ×53). *B:* Replacement of fat lobule by polymorphonuclear cells and lymphocytes with microcyst formation (H & E, ×28). *C:* Early proliferative fat cell response to inflammation of fat lobule (H & E, ×110).

observed, though giant cells are frequent. In 2 of 5 patients studied, the tuberculoid masses replaced most of the fat lobules; these were the 2 patients with septal hyalinization, fibrosis, and thickening. Vascular changes were minimal in all 5 patients.

DISCUSSION

Erythema nodosum is an easily defined clinical disease, as illustrated by the studies of Hellerström

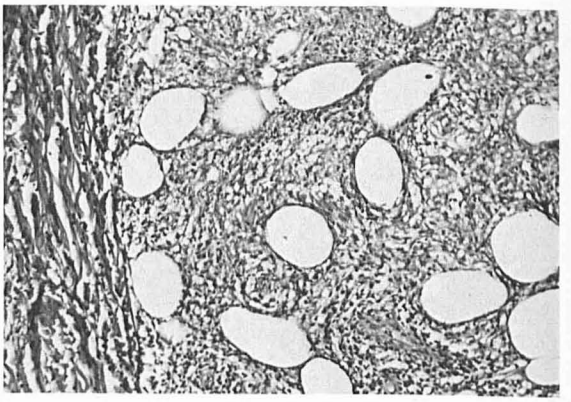

FIG. 4. Histiocytic-granulomatous panniculitis in erythema nodosum (H & E, ×110).

TABLE II. *Clinical syndromes of erythema nodosum*

Nodular erythema
Acute
Chronic
Migratory
Erysipeloid erythema
Thrombophlebitis
Acute panniculitis

[11] and of Hannuksela [2], but because of the many histiopathologic features showing involvement of the vessels, septa, and fat lobules in acute, subacute, and chronic inflammation with hemorrhage and fibrosis, the microscopic findings often are not compatible with the clinical diagnosis. For instance, a clinician may take a biopsy specimen in erythema nodosum and receive a histopathologic diagnosis of acute panniculitis, thrombophlebitis, granulomatous or nodular vasculitis, or migratory panniculitis. Each of these diagnoses has a distinct and separate implication for the clinical expression and prognosis of disease, and yet each has a histopathologic picture similar to that in erythema nodosum. In erythema nodosum, there is some correlation between the clinical manifestations (Tab. II) and the histologic patterns (Tab. I). The interpretation of the subcutaneous histopathology may be simplified by examination of the rare cases in which the veins or fat lobules may be principally involved. The blood vessels involved in superficial thrombophlebitis are much larger than the muscular veins, which become inflamed in atypical erythema nodosum. The acute panniculitis in erythema nodosum is focal and related to the vessels or is associated with hemorrhage.

Some patients with erythema nodosum develop individual lesions that may last for several months, to which the term "chronic erythema nodosum" can be applied and contrasted with the common or acute recurrent erythema nodosum. Fine and

Meltzer [12] proposed that chronic red nodules with focal granulomatous histologic features be called "chronic erythema nodosum." Bäfverstedt [13,14] and Vilanova and Pinol Aguadé [15] discussed migratory panniculitis as a separate entity because of the clinical and histologic findings. The clinical presentation of the chronic spread of nodular inflammation is a unique clinical response that clinicians must recognize, but we [10] agree with Fine and Meltzer [12] and with Hannuksela [2] that the granulomatous septal inflammation invading the fat lobules also may be found in erythema nodosum. Hannuksela's [16] study of 56 cases of erythema nodosum migrans gives specific support to the unity of the acute, chronic, and migratory forms of erythema nodosum because the histopathologic changes were compatible with those of erythema nodosum (accumulations of lymphocytes, histiocytes, and occasional giant cells in the septum of fat lobules and between fat cells). Perry and Winkelmann [17], using the microscopic criteria of septal granuloma formation, found that 4 of 14 patients with these histologic changes had clinically typical erythema nodosum. One of the 14 patients had clinically and histologically migratory panniculitis, but the lesions were of such short duration that erythema nodosum was considered the likely diagnosis. Hannuksela [2] observed that both migratory and typical erythema nodosum had the same spectrum of causative agents. Contraceptive hormone medication frequently was related to nodules of longer duration, as were sarcoidosis and unknown causes whether the clinical pattern was the chronic, migratory, or typical form of erythema nodosum. Therefore, septal granulomas do occur in erythema nodosum and, together with the rare cases of granulomatous panniculitis, define a unique histopathologic and clinical evolution of the erythema nodosum problem. This chronic evolution is probably related more to host response than to antigen source.

The cause of erythema nodosum is still debated. For instance, some authors consider erythema nodosum a vasculitis or an inflammation of the arteries. Studies with immunofluorescence have failed to reveal the findings associated with the immune complex pathogenesis of necrotizing or "allergic" vasculitis. The evidence for considering erythema nodosum as a delayed hypersensitivity cellular response of the vessels, principally to microbiologic or other antigens, appears to be significant. The histopathologic findings support this position, as does the occasional relationship of erythema nodosum to erythema multiforme. The major dermal and subcutaneous inflammation is lymphocytic. The production of delayed hypersensitivity, superficial phlebitis, and erythema nodosum may be seen in the same patient, indicating that (whether the cause is an organism such as *Mycobacterium tuberculosis* or an inflammatory disease such as Behçet's syndrome) lymphocytic vascular inflammation may also produce the acute polymorphonuclear leukocytic and thrombotic inflammation of medium or large vessels, septa, and fat. This seems reasonable but remains unproved. Two types of erythema nodosum may exist, based on the pathologic findings. One type is an acute, vascular, and septal leukocytic inflammation and panniculitis, and the other type, which has the same clinical picture, is a delayed hypersensitivity lymphocytic acute inflammatory involvement of the same portions of the skin. The immunologic and clinical data, plus the histologic findings of mingling, suggest that these are not two separate microscopic definitions of two pathogenetic processes but rather are variations in the intensity of the host-tissue inflammatory response to the delayed hypersensitivity reaction of the vessels.

Acute panniculitis is considered to be equivalent to the first stage of Weber–Christian disease. We found that most patients with this histopathologic diagnosis have erythema nodosum, and this should help us understand many instances in which either term is used. The clinician can ignore the pathologic report that suggests severe disease in his patient who has short-lived, red nodules of the lower legs. Similarly, the dermatopathologists will find it easier to understand acute panniculitis if most of the cases considered are erythema nodosum and if the histopathologic findings can be labeled as such. Some of our other cases of acute panniculitis, which earlier might have been labeled Weber–Christian disease, have been related to the syndrome of acute panniculitis with or without fat necrosis or pancreatic disease and have been associated with amylase or lipase (or both) in the lesions, as well as in the blood or urine. The demonstration of the second stage of Weber–Christian disease, that of lipocyte proliferation (proliferative atrophy), in erythema nodosum further emphasizes the lack of specificity in the histologic features of this entity. The final stage of fibrosis in Weber–Christian disease has no specificity at all.

The granulomatous panniculitis observed in erythema nodosum is also consistent with the concept of delayed hypersensitivity cellular inflammation. The reaction is lymphohistiocytic in part, and granuloma formation is a natural end point of cellular immune responses. The differential diagnosis of this histologic–clinical pattern further indicates that the delayed immune-response mechanism must be seriously considered. The syndromes of erythema induratum, nodular vasculitis (nontuberculous erythema induratum), tuberculoid leprosy, and sarcoid indicate that granulomatous erythema nodosum might be considered a tuberculoid histologic response of the subcutaneous tissue to one of the many types of antigens through the delayed hypersensitivity mechanism.

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